SCIENCE

A WEEKLY JOURNAL DEVOTED TO THE ADVANCEMENT OF SCIENCE, PUBLISHING THE OFFICIAL NOTICES AND PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

FRIDAY, APRIL 24, 1908

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THE AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

SECTION K—PHYSIOLOGY AND EXPERIMENTAL MEDICINE

SUMMARY OF THE PROCEEDINGS

THERE were four meetings of the section at the University of Chicago during convocation week, as follows:

First Meeting.—Manual Training School Building. Tuesday afternoon, December 31, 1907. Presiding officer: Vice-president Ludvig Hektoen. A large audience was present to hear the address of the retiring Vice-president, Simon Flexner, on "Tendencies in Pathology." (See SCIENCE, XXVII., p. 128, 1908.)

Second Meeting.—Physiology Building. Tuesday afternoon, December 31, 1907 (immediately after the adjournment of the first meeting). Joint session with the American Physiological Society. Presiding officer, Frederic S. Lee. Eight papers were read. (See the scientific proceedings.)

Third Meeting.—Reynolds Club Theater. Wednesday afternoon, January 1, 1908. Presiding officer, Vice-president Ludvig Hektoen. This session was devoted to a symposium on *Immunity* (see the scientific proceedings) and to the election of officers and other executive matters (see the executive proceedings).

Fourth Meeting.—Reynolds Club Theater. Thursday afternoon, January 2, 1908. Presiding officer, Charles E. Marshall. Joint session with the Society of

American Bacteriologists. Six papers were read. (See the scientific proceedings.)

EXECUTIVE PROCEEDINGS

The following officers were elected for the year 1908–9:

Vice-president of the Association and Chairman of the Section—William H. Howell.

Secretary—William J. Gies.

Sectional Committee—Ludvig Hektoen, vice-president, 1907–8; William H. Howell, vice-president, 1908–9; William J. Gies, secretary, 1905–9; J. McK. Cattell (one year); Frederick G. Novy (two years); Graham Lusk (three years); Jacques Loeb (four years); Charles S. Minot (five years).

Member of the Council—Edwin O. Jordan.

Member of the General Committee—H. T. Ricketts.

The following resolutions relative to research in tropical medicine were presented by the secretary, were unanimously recommended for consideration by the association and were ultimately endorsed by the association in general session:

WHEREAS: There exists at the present time in Panama an extraordinary opportunity for research work in certain phases of tropical medicine, through the existence there of well-equipped hospitals and well-trained medical men under the supervision of an expert sanitarian, himself a member of the Isthmian Canal Commission, and

WHEREAS: The solution of problems connected with this branch of medicine is of the highest importance to the welfare of this and other countries, be it

Resolved, That it is the sense of the American Association for the Advancement of Science that Congress at its present session should appropriate funds for the purpose of establishing a research laboratory on the Isthmus, to be devoted to the solution of existing problems in tropical disease.

SCIENTIFIC PROCEEDINGS

First Meeting.—Vice-presidential address: "Tendencies in Pathology," Simon Flexner. (Published in SCIENCE, this volume, p. 128.)

Second Meeting.—Papers in joint session with the American Physiological Society.

Program

"A Comparative Study of the Cilium as a Key to the Structure of Contractile Protoplasm," by C. F. Hodge and O. P. Dellinger.

"Daily Life of *Amœba proteus*," by C. F. Hodge, D. Gibbs and O. P. Dellinger.

(1) "The Reaction of *Amœba* to Stimuli of Small Area," (2) "The Effects of Prolonged Centrifugal Force on *Paramœcium*," by J. F. McClendon (by invitation).

"The Relation of Plasticity to Age in the Dancing Mouse," by R. M. Yerkes.

"The Bacterio-agglutinating Action of Lymph under Different Conditions of Lymph Formation," by B. Brande (by invitation).

"The Relative Hemolytic Action of Serum and Lymph under Different Conditions of Lymph Formation," by T. Hughes (by invitation).

"The Effect of Stimulation of the Vagi upon the Onset and Development of Rigor Mortis of the Mammalian Heart," by S. J. Meltzer and D. R. Joseph.

"The Osmotic Concentration of the Blood during Anesthesia," by A. B. Luckhardt (by invitation).

Third Meeting.—Symposium on Immunity.

Program

Introductory remarks by the chairman, Ludvig Hektoen.

"A Review of Anaphylaxis, with Especial Reference to Immunity," by M. J. Rosenau and John F. Anderson.

"Hypersusceptibility and Immunity," by Victor C. Vaughan.

"The Hemolysins of Animal Toxins," by Preston Kyes.

"The Differentiation of Homologous Proteins by Serum Reactions," by S. P. Beebe.

"On Spirochetal Immunity," by Frederick G. Novy and R. E. Knapp.

"Immunity in Rocky Mountain Spotted Fever," H. T. Ricketts and L. Gomez.

"Artificial Immunity to Glucosides," by William W. Ford.

"Virulence of Pneumococci in Relation to Phagocytosis," by E. C. Rosenow.

"The Mechanism of Streptococcus Immunity," by Gustav F. Ruediger.

"Immunity in Tuberculosis," by Mazÿck P. Ravenel.

"Chemical Aspects of Immunity," by H. Gideon Wells.

General discussion, in which many of the members participated.

ABSTRACTS OF IMMUNITY PAPERS

A Review of Anaphylaxis, with Especial Reference to Immunity: By M. J. ROSENAU and JOHN F. ANDERSON.

Anaphylaxis (ἄνα against, and φυλός guard or φυλάξις protection), also called the Theobald Smith phenomenon, hypersusceptibility, supersensitiveness, is a condition of unusual or exaggerated susceptibility of the organism to foreign substances. Anaphylaxis may be congenital or acquired; it is specific in nature. The condition of anaphylaxis may be brought about by the introduction of any strange protein into the body. Hypersusceptibility to proteins that are non-poisonous in themselves may readily be induced in certain animals.

An animal may be in a condition of hypersusceptibility and immunity at the same time. The two conditions are closely interwoven. The one may be dependent upon the other. Pirquet advises that the term *immunity* be limited to indicate the condition of complete resistance in which no clinical reaction occurs, when poisons (such as diphtheria, tetanus, etc.) are introduced into the organism. He suggests the term "Allergie" to indicate conditions of acquired immunity associated with anaphylaxis, such as that induced by vaccinia against variola, that of the luetic against syphilis, or of that produced by one attack of some of the acute specific infections. This condition of allergie manifests itself in the renewal of the infection in an entirely different manner from the reaction to the primary infection.

The tuberculin and mallein reactions are well-known instances of anaphylaxis. These substances are not poisonous when introduced into a healthy individual, but the tuberculous individual is anaphylactic to tuberculin and an individual suffering with glanders is in a state of hypersusceptibility to mallein.

The best studied instance of anaphylaxis is that produced in the guinea-pig by the injection of a foreign protein, for example, horse serum, egg white, milk, etc. Especial study has been made of the anaphylactic reaction of the blood serum of the horse, partly because that serum is so much used in serum therapy.

The first injection of horse serum into the guinea-pig sensitizes it to a subsequent injection of horse serum. A definite time must elapse—about eight or ten days—between the first and the second injections. A very minute quantity given at the first injection is sufficient to sensitize a guinea-pig.

The reaction is specific in nature. Guinea-pigs may be in a condition of anaphylaxis to three protein substances at the same time. The guinea-pig differentiates each anaphylactic-producing protein in a distinct and separate manner. This adds weight to our belief that profound chemical changes, perhaps in the central nervous system, constitute the essential features of the phenomenon rather than morphological alternations.

Hypersusceptibility to horse serum is transmitted from the mother guinea-pig to her young.

There are certain analogies between the action of tuberculosis (tuberculin) and serum anaphylaxis.

Guinea-pigs may be actively immunized against anaphylaxis. The immunity, however, can not be transferred passively to other animals in the blood serum or body juices.

Hypersusceptibility has an important bearing upon the problems of immunity. Anaphylactic symptoms may be produced in guinea-pigs by the protein extracts obtained from bacterial cells. In the case of

typhoid and colon bacilli this is followed by a definite immunity. In the case of anthrax, however, immunity does not follow hypersusceptibility to the anthrax protein. We are therefore not dealing with a general law applicable to all infections, but with certain limitations as in the case of antitoxic immunity.

Hypersusceptibility and Immunity: VICTOR C. VAUGHAN.

In order that I may be correctly understood I wish to state at the beginning that in my opinion the mechanism of immunity to all infections and intoxications is not the same and the time has come when it is well for us to distinguish between the different forms of immunity. I believe that there is already sufficient ground to justify us in holding that there are at least three forms of immunity and these I would designate as follows:

1. *Antitoxin Immunity.*—The poison to which this form of immunity may be secured are the venom of serpents, the vegetable poisons, abrin and ricin, and the toxins of bacillus diphtheriæ, b. tetanus and b. botulinus. Possibly others may be added to the list. These poisons certainly belong to a distinct group. They resemble ferments in three striking particulars: (*a*) in aqueous solution they are destroyed by a temperature of 100° or less; (*b*) they are active in solutions so dilute that they do not respond to the three most characteristic proteid color reactions, the biuret, Millon and Molisch tests; (*c*) animals treated with successive doses at short intervals develop anti-bodies. For the present at least Ehrlich's theory must be regarded as the most satisfactory explanation of this form of immunity. There is no proof, so far, that either phagocytic action or proteid cleavage has anything to do with the production of this form of immunity.

2. *Phagocytic Immunity.*—This form of immunity has been most thoroughly studied with the cocci, and as we are to have two papers on it to-day I will refrain from expressing any opinion of my own on the subject.

3. *Lytic Immunity.*—This is generally designated as bactericidal or bacteriolytic immunity, but there is serious objection to the employment of either of these terms, for the following reasons: (*a*) bacterial proteids are not the only proteids that may be and are split up in the animal body. Most foreign proteids when introduced into the circulation directly and without previous subjection to the digestive juices undergo specific proteolysis, and this is true whether these proteids are living or dead. (*b*) The cleavage of poisons in the body is probably not confined to those of proteid composition. (*c*) The term bactericidal is inappropriate because the bacteria may be so altered chemically that they are robbed in part or wholly of their harmful properties and still are not killed. Examples of the persistence of specific bacteria in the body after recovery from the disease are well known and immunity to disease may coexist with the specific bacteria of that disease still living in the body. The bacterial proteid owes its poisonous action to its molecular structure and this may be so modified as to render the organism a comparatively harmless guest without destroying its life. (*d*) The term bacteriolysis is certainly inappropriate, first because all these poisons are not bacterial and second because the word bacteriolysis means that the bacterial cell is destroyed, and we have just seen that this does not happen in all cases. In view of the facts here briefly condensed I prefer the word "lytic" to designate this form of immunity. I am not altogether satisfied with

this term and hope that some one will suggest a better.

I desire it plainly understood that in what I am to say to-day about hypersusceptibility and immunity I am speaking exclusively of what I have designated as "lytic immunity." The following statements are based largely upon work done in my own laboratory and I will condense as much as possible; and in doing so my statements may seem dogmatic, for I can not take the time to prove each of them, but such proof may be found in the papers that have been published by my students and myself.

All true proteids contain a poisonous and a non-poisonous group and can be split into these groups by the action of dilute alkali in absolute alcohol at 78°. The presence of the amino-acid tyrosin is apparently essential to the poisonous group, and those albuminoids, such as gelatine, that do not contain tyrosin yield no poisonous group. So far we have tested more than twenty different proteids, bacterial, vegetable and animal, and all that contain the tyrosin group yield a poison. Please understand that I do not claim that tyrosin is the poisonous group, but I believe it to be a constituent of the poisonous body. The poison does not contain a carbohydrate or a nuclein group, the absence of the latter being demonstrated by the complete absence of phosphorus. The non-poisonous group consists largely of nuclein, the carbohydrate being a sub-group in the nucleic-acid molecule.

The poisons obtained from these different proteids, although not identical, are similar and probably owe their poisonous action to the same or similar atomic arrangement. Much of the poison is destroyed by our crude method of obtaining it. The effect of the poison on animals is characteristic or pathognomonic and manifests itself in three stages. The first is a period of peripheral irritation manifesting itself in animals by violent scratching and in man by itching, erythema or urticaria. The second may be designated as the period of depression with or without partial paralysis. The third or convulsive stage is characterized by more or less violent clonic convulsions, generally beginning with opisthotonos and terminating in death. These symptoms are identical both in character and in sequence whether induced in a fresh animal by the injection of the free poison or in a sensitized animal treated with the unbroken proteid. When a non-lethal dose of the free poison is given, the first and second stages only appear, and the same is true when a non-lethal dose of the unbroken proteid is administered to a sensitized animal. The proteid contains the poison, which can be extracted by chemical means. The free poison and the unbroken proteid in appropriate animals induce the same symptoms, in the same sequence and in the same time. There is therefore no more doubt that the animal that dies from the free poison and the one that dies from the unbroken proteid die from the same poison than there is that the man who dies from morphine and the one who dies from opium die from the same poison. The poisonous portions of these proteids produce no antibodies when repeatedly injected into animals, and only slightly increase the tolerance for themselves. Likewise they slightly increase tolerance for the unbroken proteid in sensitized animals. Even in this, however, their action is not specific. It seems evident from these findings that the poisonous or the toxophore group in the proteid molecule plays no part in the production of lytic immunity. In this respect the production of lytic and antitoxic immunity agree, but in the former there is no antitoxin formed.

When a foreign proteid is injected into an animal and a certain interval of time is allowed to elapse, a second injection of the same proteid is likely to cause the development of untoward symptoms and possibly death in a short time. These symptoms are exactly those which I have described as being due to the free poison, and I can see no reason for doubting that they are due to the same poison which is set free in the animal body by a cleavage process giving analogous but much more perfect results than those obtained by the action of alkali and alcohol in the retort. With some proteids, the first or sensitizing dose need not be the unbroken proteid, but its non-poisonous or haptophore group. For instance, the haptophore group of the egg-white molecule sensitizes to unbroken egg-white quite as well as the unbroken molecule itself does. If the proteid of the colon or typhoid bacilli be split into haptophore and toxophore groups and animals be sensitized with the former, such animals will bear several times the ordinarily fatal dose of the homologous living bacillus. An animal sensitized with the haptophore group of a dead proteid dies on the subsequent injection of the same proteid in unbroken form, provided that the time interval between these injections has been a certain minimum or greater, this minimum varying with different proteids. An animal sensitized with the haptophore group of the colon or typhoid bacillus survives a subsequent inoculation with the living homologous bacillus. These results have struck observers as being antipodal and so they may seem, when in one instance death results in an animal apparently perfectly normal and, in the other, an animal treated with a fatal dose of toxicogenic bacterium remains unaffected. The animal that has been previously treated with the egg-white haptophore is said to be in a state of hypersusceptibility or in an anaphylactic state (without protection), while the one that has received the bacterial haptophore is said to be immune. Yet, a close study of these two sets of phenomena will, I think, convince any one that the apparently antipodal are in reality identical. In both the process is certainly identical and consists in the cleavage of the molecule of the foreign proteid and the liberation of the toxophore group. How has the one animal been sensitized or brought into this state of hypersusceptibility and how has the other been immunized? Both of these conditions have been brought about in the same manner; indeed the processes are identical. In both there has been developed in certain cells in the animal body a specific zymogen, which on the second treatment is converted into a proteolytic ferment, and this splits up the proteid into its poisonous and non-poisonous groups. The animal treated with the second injection of egg white is not killed unless the proteid given is sufficient in quantity to yield a fatal dose of the toxophore when it is split up, and the animal immunized to the typhoid bacillus is certainly killed if the inoculated bacilli be sufficiently numerous to yield a fatal quantity of the toxophore when their proteid substance is split up. Ordinarily more than a fatal dose of the dead proteid is administered at the second treatment and the animal promptly dies. What we call the minimum fatal dose of a bacterial culture does not contain enough toxophore to kill the animal, even without any acquired immunity, but it develops that amount during what we call the period of incubation, which in guinea-pigs inoculated with colon or typhoid bacilli means generally from ten to twelve hours. Now, it must be evident that if the proteid substance of the injected bacilli be split up before the living organisms have time to develop a fatal amount of the toxophore, the animal does not succumb to the inoculation and

is said to be immune. By carefully regulating the size of the second dose one can develop in both the egg-white and the typhoid animals the first and second stage of the symptoms of proteid poisoning without reaching the convulsive stage.

The effect of the poison depends not only upon the amount set free, but also upon the rapidity with which it is liberated. The poison kills by its action on the respiratory center. This is demonstrated (1) by the continued beating of the heart for some minutes after respiration has ceased, (2) by the symptoms which are those of asphyxiation, and (3) by the post-mortem findings, such as a fluid state of the blood and the engorgement of certain internal organs with ecchymoses, as found by Gay and Southardt. I infer that the poison does not destroy the cells of the respiratory center, but puts them out of commission or interrupts their normal function. The basis for this inference is the ready and apparently complete recovery of animals after manifesting the first and second stages of poisoning. Recovery after the development of the convulsive stage occurs but rarely. My reason for concluding that lytic immunity consists in the development of a proteolytic ferment is founded upon what seems to me a demonstrated fact that the symptoms are due to a cleavage of the proteid molecule into a haptophore and a toxophore group, and we know of no agents in the animal body save enzymes that are capable of splitting up proteids. I am inclined to the opinion, subject, of course, to change with additional knowledge, that the cells that become sensitized and in which the zymogen is stored are connective tissue cells and that in order to be sensitized they must come into direct contact with the haptophore group of the proteid, and the presence of the same group is necessary to convert the zymogen into an active enzyme. I think it most probable that the sensitization of a cell consists in causing a rearrangement in the molecular structure of some one of its proteid constituents. Sensitization may be local or general; it can exist only in those tissues that have come under the direct influence of the haptophore. This explains why the soluble haptophore split off from the bacterial cell is more efficient both in sensitizing and in activating the body cell than is the unbroken bacterial cell. Typhoid bacteria introduced into the abdominal cavity of an unsensitized animal may be acted upon by phagocytes, but no lytic action takes place until the body cells have been sensitized by the bacterial proteid; and their sensitization is at first local. When a coagulated proteid is injected into the peritoneal cavity of a sensitized animal the lytic action is local and the phenomenon of hypersusceptibility is never manifested, except when the activating dose is introduced into the animal in soluble form; then a large number of cells are activated at once, the proteid is split up with explosive rapidity and the poison, being set free in the circulating blood, reaches the respiratory center promptly and death as a rule follows speedily. The striking experiments of Pirquet with vaccination are, according to my interpretation of them, beautiful examples of local sensitization and consequently of local reaction. The same is, I think, true of the Calmette eye reaction with tuberculin. In some tubercular individuals the tissue of the conjunctiva has become sensitized by the split products resulting from the breaking up of the tubercle bacilli and the first application causes a reaction. But the same thing is shown more strikingly when the eye of a non-tubercular individual is sensitized by a first application and then activated by a second when the reaction is prompt, sometimes quite violent, and confined sharply to the parts touched by the first application.

I believe that lytic immunization will prove in the near future of great service not only in affording protection, but in the treatment of some infectious diseases, yet it will be well to understand at the outset that it will have its limitations and also its dangers. We can not hope for the high degree of protection that is secured by the antitoxic treatment of diphtheria. From my experiments upon animals with the haptophores of the colon and typhoid bacilli I believe that an immunity to from ten to twelve times the minimum fatal quantity of the living bacillus is as much as we can reasonably hope.

The Differentiation of Homologous Proteins by Serum Reactions: S. P. Beebe.

It is now admitted by all laboratory workers in the field of immunity that one can differentiate between the proteids of different species of animals by means of serum reactions. Such reactions are not absolutely specific, as it is well known that closely related species of animals show a mild reaction, but in point of time and completeness of the reaction it is possible to differentiate sharply between species.

With homologous proteids there is no such unanimity of opinion, although comparatively little work has been done. The serum reactions are capable of showing differences in structure which we can not demonstrate by other means, and it seems reasonable to believe that we may be able to differentiate between proteids from the same species, but from organs having widely varying functions, such as the liver and the kidney. For the purpose of developing the anti-serum the nucleoproteids of these organs have been injected into alien species of animals. The nucleoproteids were chosen because they are readily prepared and because they probably represent the most important of the cell constituents. By means of such serum one may obtain precipitin and agglutinin reactions, which are specific in the same sense that heterologous reactions are specific.

On Spirochetal Immunity: F. G. Novy and R. E. Knapp.

The question of the plurality of species of spirilla in relapsing fever, raised by us two years ago, has been answered since in the affirmative, for we now have four, and possibly five, essentially distinct strains in human relapsing fever. These several species, strains or varieties are:

S. Obermeieri—origin, Moscow, Uhlenhuth and Haendel.

S. Novyi—origin, New York, Norris.

S. Kochi n. sp.—origin, East Africa, Berlin, Koch.

S. Duttoni—origin, West Africa, Runcorn, Dutton and Todd.

S. Carteri—origin, Bombay.

The specific differences for the first four have been fully established and it is quite certain that when direct comparative tests are made with the Bombay spirillum this will also be found to be distinct. In view of these facts it may well be asked whether a still greater number of strains will not be found when further comparisons are made with the spirilla from different parts of Russia, Africa, Asia and America. From our studies on the immunity reactions of the first four spirilla we are inclined to believe that such will be the case and that a considerable number of apparently different species or strains will be discovered. The necessity for recognizing this condition of affairs will be apparent, for, as will be shown, the curative action of the serum of an animal immunized to one strain is manifested only in animals infected with that particular organism and is without appreciable effect upon the other strains.

The four strains in the order as listed above show a marked gradation of properties. This is seen in the duration and severity of the initial attack, in the frequency and intensity of relapses and in the

mortality following upon the injection of a uniform dose of 0.25 c.c. of spirillar blood, the infection with *S. Obermeieri* is mildest with barest indication of relapses and that with *S. Duttoni* is most severe; death usually results, or relapses occur regularly and are repeated, time and again. In general, the four spirilla can be readily separated into two groups, the Moscow and New York strains falling together, while the two African strains are more closely allied than with either of the others. In the African strains a notable feature is the peculiar massing of red-blood cells, which feature enables one by mere microscopic examination of the fresh blood to decide which of the two groups is concerned. There are also differences in size, the African group showing spirilla which are fully twice as long as those of the first group. A full discussion of the differences will be taken up elsewhere.

The study of the immunity or serum reactions of these four strains of spirilla presents interesting facts regarding their relationship and incidentally brings up the question of the value of the so-called specific reactions as a reliable means for the differentiating of species. The question as to what constitutes a species, itself a difficult one in connection with the higher forms of life, becomes far more difficult to answer when it concerns the unicellular organism which seemingly is incapable of presenting any fixed characteristic. Variation in the ordinary morphological and biological properties is the rule among protists and the serum reactions which are looked upon as the most specific characteristics seem to offer no exception. The differences in these reactions must be considered as an expression of changes in the molecular composition of the living protoplasm, and for each set of new conditions a new equilibrium in the arrangement of atoms must be established. The known examples of tautomerism among the relatively simple organic compounds may serve to illustrate the conception as applied to living matter.

In a previous paper we clearly demonstrated the preventive and curative action of the serum of animals immunized to the New York spirillum, and it was, therefore, desirable to ascertain whether similar results could be obtained, under like conditions, with the other three strains. Without going into unnecessary detail at the present time, it may be said that the serum of an immunized rat exerts a prompt curative action in rats infected with the corresponding or homologous spirochete, and that in like dosage it is without effect upon the remaining three organisms. This fact can best be seen from the following table:

TABLE I

Curative Experiments with Immune Sera

Rats infected with	Effect of 2 c.c. of serum of rat hyperimmunized with			
	S. Obermeieri.	*S. Novyi.*	*S. Kochi.*	*S. Duttoni.*
S. Obermeieri	+ cure	+ cure	——	——
S. Novyi.	——	——	——	——
S. Kochi.	——	——	+ cure	——
S. Duttoni.	——	——	——	+ cure

It will be seen from the above that of four rats infected with *S. Obermeieri,* and containing at the time large numbers of spirilla in the blood, the one which received the serum from a rat hyperimmunized to that organism was promptly cured, whereas the sera of the other hyperimmune animals were without any apparent effect. A like specific curative action is obtained with the other organisms when the homologous serum is used. By a "cure" is meant the total disappearance of the spirilla from the peripheral blood in from one half to four or six hours. This curative effect may be permanent or it may be followed by a slight relapse in the course of seven or ten days.

Such relapses are practically absent with the Moscow strain, very slight with that of the New York and more common with the African strains.

In the case of *S. Duttoni* the "cure" is not always as marked as with the other three, depending as it does, first, upon the dose and efficiency of the serum employed, and, second, upon the stage of infection. The latter is a most important factor. Rats in the early stage of infection with this organism (that is, on the first day following the injection of spirilla) are readily cured within half an hour without any untoward effect. The administration of the serum on the second day of the disease, at a time when the blood is swarming with spirilla, leads to agglutination and solution of such masses of organisms that death from intoxication and obstruction is the usual result. When the animal survives, the spirilla may continue to persist in somewhat lessened numbers. This latter fact is due to the presence of "immunized" or "serum-fast" spirilla. Hence, in the treatment of this disease it is not advisable to employ a curative serum, in large doses, at the time of maximum infection.

The *S. Duttoni* is especially prone to reciprocal immunization, since this organism can be found at times in large numbers, in the blood of hyperimmunized animals. This serum-fast property, first demonstrated for *S. Kochi* by Levaditi and Roché, is especially marked with *S. Duttoni,* and the recognition of this state offers a most rational explanation of the cause of ordinary relapse as well as that following the curative treatment. Hitherto it was believed that the relapse was due to the survival, in extravascular spaces, of spirochetes which after the partial destruction or elimination of the specific antibodies were able again to invade the circulation. In the light of the facts now known it is clear that the relapse is due to the survival of a few individuals which have acquired more or less immunity to the specific germicidal bodies elaborated in the infected animal. As a result a new "serum-fast" strain develops, which in turn calls for a new anti-body. The latter is apparently not as active as the first, or is more unstable, or is more readily eliminated, and hence the continuance of the relapses with this organism. This adaptation of spirilla would appear to be least marked with the Moscow spirillum, since with it relapses in rats are scarcely recognizable. On the other hand, *S. Duttoni* is at the other extreme, and from what is known of the mortality in the Bombay fever, it may be inferred that the *S. Carteri* will be found to be even more prone to relapse in rats.

As pointed out by Levaditi, the serum-fast character is perhaps a fixed property of *S. pallidum,* and without doubt this conception accounts for the persistence of that organism within man better than any other theory. The difficulty of producing a curative serum for the syphilitic spirochete will be readily seen. The phenomenon of reciprocal immunization is not limited to this group, for, indeed, it was first recognized in the study of trypanosomes. Neither can it be adduced as a characteristic of protozoa, for like conditions are now known to exist with various bacteria, and this fact must, therefore, be taken into consideration in the treatment of bacterial disease with anti-sera. Many data are now at hand which go to show the existence of a plurality of strains for nearly every pathogenic organism. And, moreover, such modifications must be expected if we assume, as there is good reason to, the existence of labile groups in the living molecule.

The practical application of the curative action of a given immune serum, it will be seen, is restricted to the infection caused by the corresponding spirochete, and hence

the need of an exact diagnosis as to kind of spirillum present. The use of a polyvalent serum, obtained from animals immunized to all four strains (and more), as can readily be done, will perhaps be desirable, especially in localities where several strains are known to occur. At present the one obstacle in the way of a realization of a perfect means for the prevention and cure of the various forms of relapsing fever is the failure to obtain artificial cultures of the spirochetes.

While the curative experiments indicate a marked specific action of each serum, this specificity disappears to a certain extent when the serum is used for preventive purposes. It will then be found that a given serum may prevent or modify the infection by two or more strains and this fact must be interpreted as indicating a close relationship of such strains. This conclusion is further borne out by cross-immunization experiments with recovered or hyperimmune animals. Certain it is that the differences between any two spirochetes, as, for example, Moscow and New York, is no greater than between *S. Duttoni* and its serum-fast strain.

TABLE II

Prevention Experiments with Immune Sera

Rats infected with 0.1 c.c. spirillar blood.	Effect of 1 c.c. of serum of rat hyperimmunized with			
	S. Obermeieri.	*S. Novyi.*	*S. Kochi.*	*S. Duttoni.*
S. Obermeieri	+	+	± slight action	± very slight action
S. Novyi.	± decided action	+	± decided action	—
S. Kochi.	—	—	+	+
S. Duttoni.	—	—	—	+

From the above table it will be seen that while a given serum has a perfect preventive action with respect to its own strain, a more or less like action is exhibited with reference to the nearest strain. The + sign shows full protection, whereas the ± indicates considerable action as revealed by delayed or mild infection. With a larger amount of serum an even more marked overlapping of immunity can be expected, and this is what actually is observed when cross-infection is attempted into recovered or hyperimmunized rats. The large amount of immune blood in these animals ensures a greater preventive action, as will be seen by comparing Tables II. and III.

TABLE III

Prevention in Hyperimmunized Rats

Rats infected with 0.25 c.c. spirillar blood.	Effect in rats hyperimmunized with			
	S. Obermeieri.	*S. Novyi.*	*S. Kochi.*	*S. Duttoni.*
S. Obermeieri	+	+	+	+
S. Novyi.	+	+	+	—
S. Kochi.	—	—	+	+
S. Duttoni.	—	—	—	+

The details of all these and other experiments must of necessity be omitted at the present time. The facts given, however, clearly show that in relapsing fever we are dealing with a group of related organisms which, while in one sense they can be regarded as distinct species, after all must be considered as derived from one stem. Further comparative studies must show whether or not this variation is even more common than is indicated by the known four strains. As to the determining factors which bring about these modifications nothing definite can as yet be stated, though the conditions involving the preservation of the virus, as pointed out by Marchoux for the chicken spirochete, may be of prime importance.

Immunity in Rocky Mountain Spotted Fever: H. T. RICKETTS and L. GOMEZ.

An attack of Rocky Mountain spotted fever, produced experimentally in the monkey or guinea-pig, is followed by strong and prolonged immunity to second inoculations. The offspring of an immune female guinea-pig are immune and their immunity

does not depend on the ingestion of immune milk.

Immune defibrinated blood in doses of 0.1 c.c. to 0.3 c.c. protects against twenty to forty times the minimum pathogenic dose of infected blood, the two being mixed before injection. One cubic centimeter of immune blood given subcutaneously protects against 20 to 40 minimum pathogenic doses of virus given subcutaneously 10 to 15 days later. This passive immunity may have a longer duration, since its limits have not yet been determined accurately.

The immune blood has little curative power when spotted fever is well established, but when given early and in sufficient quantity will shorten the course of the fever by three or four days.

Vaccination of guinea-pigs may be accomplished by a single injection or by two or more injections of immune blood mixed with virus in appropriate quantities, with the result that two months later they resist infection by twenty to forty pathogenic doses of the virus. The immunity of vaccinated guinea-pigs finds expression in the strong protective power of their blood when the latter, mixed with virus, is injected into normal guinea-pigs.

The results indicate that immune serum may be effective in preventing spotted fever in man, provided that it is given within a reasonable time following the bite of an infected tick.

It is also hoped that the vaccination method will be sufficiently satisfactory and safe to warrant its use in preventing spotted fever in man. Its value is yet to be proved on the monkey.

The nature of the anti-bodies has not been definitely established.

Artificial Immunity to Glucosides: William W. Ford.

In considering the subject of artificial immunity to glucosides, as compared with the immunity produced by the injection of poisonous proteids it should be emphasized that bacteriologists employ the term *poisonous proteids,* in a rather indefinite way, hardly ever approved of by the physiological chemists. The designation *poisonous* or *toxic proteids* or *toxalbumins* is thus applied to a group of substances embracing the true toxins characterized by certain definite physiological reactions, but never yet isolated chemically, or obtained in any condition at all resembling chemical purity. These substances are highly poisonous to animals, produce well-marked lesions peculiar to each poison injected, act upon the animal body or show their effects upon this body only after a considerable period of incubation; and by the introduction of sub-lethal doses give rise to the production of substances in susceptible animals, which neutralize their poisonous action. They are always closely associated with proteids, and are precipitated by all the well-known proteid reagents, such as alcohol, uranium acetate, aluminium sulphate, ammonium sulphate and a number of others.

They have not thus far been separated from the proteids with which they are associated, and since the purest products hitherto obtained still give the biuret reaction and still contain nitrogen and sulphur it is concluded that these substances must be proteid or proteid derivatives. A more popular designation, *proteid-like,* or *Eiweiss-ähnlich,* while possibly less objectionable from the chemical point of view, does not obviate the difficulty resulting from the use of these chemical terms, since it is rather hard to say just what constitutes the difference between a true proteid and a proteid-like body. Although one or two authorities, notably Oppenheimer,[1] believe that the toxins are not pro-

[1] Oppenheimer, "Die Bakteriengifte," in Kolle und Wassermann's "Handbuch der pathogenen Mikroorganismen," Erster Band, s, 344.

teid, it is generally accepted that successful immunization can be carried out on animals only with substances belonging in this group, variously designated as toxic proteid, proteid derivatives, proteid-like bodies, or tox-albumins, since immunization with such elements as *arsenic*, with such alkaloids as *morphin* and *strychnin* and with glucosides like *saponin* and *solanin*, and those found in digitalis and ergot has not been accomplished. Pohl[2] indeed claimed to have so treated rabbits with solanin as to render their blood serum more antagonistic to the action of solanin on blood corpuscles than the normal rabbit's serum, but his experiments could not be confirmed by Bashford,[3] in the light of whose investigations Ehrlich[4] has become positively convinced that artificial immunization with glucosides is impossible. When we consider the large number of poisonous glucosides, already isolated with a fair degree of success, and in considerable chemical purity, with but a few of which experiments have been reported, and then take account of the vast amount of work done on the toxic proteids, it is a fair inference that to deny the possibility of immunization with glucosides is to base a broad generalization upon a relative paucity of data.

Our own observations in this field originated with the attempt to immunize animals with extracts of the poisonous fungus *Amanita phalloides*, the active principle of which had been stated by Kobert[5] some years previously to be a tox-albumin powerfully hemolytic for a great variety of corpuscles. We found that saline extracts of the fungi were highly hemolytic as Kobert had stated, and that they produced very definite lesions in animals, including extensive subcutaneous edema, hemorrhages in the serous membranes, a marked degree of fatty degeneration, and a great increase of pigment in the various organs, especially in the spleen. During the treatment of animals with these extracts we experienced no difficulty in producing an active immunity, in which the animals would withstand the inoculation of two or three times a fatal dose. The serum from these immunized animals was *anti-hemolytic*[6] in a dilution of 1/1,000 or even in one of 1/5,000. When tested upon animals, one cubic centimeter of this serum would neutralize two or three multiples of a minimum fatal dose. The most powerful serum obtained was one in which 1 cubic centimeter neutralized six or seven times a fatal dose, but this serum contained such a powerful anti-hemolysin that we were led to believe that a serum from large animals more highly immunized might prove of practical value. In a chemical investigation of the fungus in the Pharmacological Laboratory, in association with Dr. Abel[6, 7] it has since been shown that the *Amanita phalloides* contains two poisons, one hemolytic and precipitated by alcohol, the other non-hemolytic and soluble in alcohol. The presence of this latter substance, the *Amanita*-toxin had already been suspected because of the poisonous character of extracts of the fungus heated to 65° C. to destroy their hemolysin, and we found that Kobert[8] had made a similar observation, publishing it in an almost inaccessible

[2] Pohl, *Arch. internat. de Pharm. et de Ther.*, 1900, 7, p. 1; 1901, 8, p. 437.

[3] Bashford, *Arch. internat. de Pharm. et de Ther.*, 1901, 8, p. 101; 9, p. 451.

[4] Ehrlich, "Collected Studies on Immunity," New York, 1906, p. 433.

[5] Kobert, *St. Petersburger med. Wochenschr.*, 1891, 16, pp. 463, 471.

[6] Ford, *The Journal of Infectious Diseases*, Vol. III., No. 2, April, 1906.

[7] Abel and Ford, *The Journal of Biological Chemistry*, Vol. II., No. 4, January, 1907.

[8] Kobert, *Sitzungsberichte der naturforschenden Gesellschaft zu Rostock*, 1899, p. 26.

journal. It was further shown by Dr. Abel and myself that this *Amanita*-hemolysin is not a tox-albumin as Kobert had stated, since all proteid can be removed from it, by the use of freshly prepared metaphosphoric acid, and by uranyl acetate, without any appreciable impairment of its hemolytic activity. Our hemolytic solution thus treated no longer responds to any of the well-recognized tests for either native or derived proteids. Although this hemolysin has by no means been obtained in a condition of chemical purity, it must, for the present at least, be classified as a glucoside because of the following reactions which our purest substance gives.

1. It reduces Fehling's solution and ammoniacal silver solution only very slightly without previous hydrolysis with acids, and very powerfully after such hydrolysis.

2. It does not ferment with brewers' yeast either before or after hydrolysis.

3. It gives characteristic tests for pentoses with (*a*) α-napthol and sulphuric acid, (*b*) phloroglucinol and hydrochloric acid, (*c*) orcinol, hydrochloric acid, and ferric chloride. It also decolorizes an alkaline solution of potassium permanganate at room temperature, and after hydrolysis gives a yellow color with sodium hydrate.

The alcohol-soluble *Amanita*-toxin, which probably is more important in cases of poisoning in man because of its resistance to the action of heat and acids than the *Amanita*-hemolysin has been shown by Dr. Schlesinger and myself[9] to be either an *indol* or *pyrrol* derivative or an *aromatic phenol* so combined with an amine group that it readily forms an indol or pyrrol ring on fusion. This substance can be obtained free from both the glucosides and the native proteids present in the plants.

Since publishing these various observations a number of experiments have been completed which confirm our earlier conclusions and throw light upon some of our difficulties, and it is desirable at the present time to take up these further experiments in brief detail. In the first place, Dr. Kinyoun while at the Mulford Laboratories at Glenolden, Pa., was good enough to immunize a horse for me with aqueous extracts of *Amanita phalloides* and found that its serum contained anti-bodies for the poisons of this fungus of such a strength that one fourth of a cubic centimeter would neutralize the poisonous dose for a 500-gram guinea-pig. While this is of hardly more than theoretical value, in studying this serum during the past year we have found that it contains a strong and permanent anti-hemolysin operative in a dilution of 1/1,000, using as an index that quantity of hemolysin which will dissolve 1 cubic centimeter of a 5-per-cent. suspension of blood corpuscles, and this anti-hemolysin is still present, even though the serum is nearly a year old.

Again, it has been shown that both the *Amanita*-hemolysin and the *Amanita*-toxin are poisonous to small animals, the lesions produced by the latter substance being similar to those seen in fatal cases of poisoning in man. The *Amanita*-hemolysin apparently owes its toxicity entirely to its blood-making properties, the pure toxin acting as a cellular poison, producing both the hemorrhages and the fatty degeneration.

The *Amanita*-hemolysin, moreover, tends to lose its activity on heating to 65° C. for one half hour and may play but a secondary rôle in fatal cases in man, the toxin possibly being the more important principle. Various animals have been immu-

[9] Schlesinger and Ford, *The Journal of Biological Chemistry*, Vol. III., No. 4, September, 1907.

nized to the two poisons in the *Amanita*, the hemolysin and the toxin. Immunization with the hemolysin proceeds without difficulty, the animals reacting well and retaining their weight. Their serum is always powerfully anti-hemolytic, a strength of 1/1,000 being found after four or five injections. Active immunity with the toxin can also be produced, the animals resisting the inoculation of two or three fatal doses and their serum conferring passive immunity upon other animals up to a limited point. At no time, however, have we obtained a higher degree of either active or passive immunity with this portion of the fungus than with the "whole extracts." We are thus confronted with the paradoxical condition that the glucoside in the fungus for which on theoretical grounds an anti-body would be supposed to be impossible will readily stimulate animals to the production of an anti-hemolytic serum, while the non-glucosidal substance is thus far the barrier to the production of a high degree of immunity. To just such an extent as the hemolysin acts in man can we obtain an efficient antitoxin, but since the toxin is apparently more potent in this respect than the hemolysin, no practical results can possibly be hoped for until some method of obtaining a stronger serum for this fraction of the fungus can be devised.

Finally, it has seemed to Dr. Abel and myself, in view of the direct contradiction which our results bear to those of Kobert, an important matter to repeat some of our earlier observations, and we have confirmed the conclusions as to the non-proteid character of the hemolysin in *Amanita phalloides* by obtaining proteid-free hemolysins from other specimens of this fungus from New York State and from Massachusetts, thus covering in these studies three widely separated localities. The hemolysins in the fungi from these three different sources can all be completely neutralized by the serum made by Dr. Kinyoun from the Maryland fungi, a fact which further points to the identity of this substance in various examples of the plant, and its wide distribution. Indeed, no typical specimens of *Amanita phalloides* have thus far been studied in which the *Amanita*-toxin, when present, was not accompanied by this blood-laking principle.

Having thus shown that an anti-hemolysin can be made for a hemolytic glucoside, it became imperative to determine whether this was a fortuitous circumstance, dependent upon some peculiar composition of the substance employed, or whether there were not other poisonous glucosides with which animals could be successfully immunized.

The most important poison available for these studies was the active principle of *Rhus toxicodendron*, or poison ivy, from both the theoretical and practical standpoint. It had some years previously been shown by Pfaff[10] that the poison of this plant was a non-volatile oil, decomposed by heat, soluble in alcohol, ether, benzine, chloroform, etc., but insoluble in water. The name *Toxicodendrol* was given to this oil. Subsequently Syme[11] has concluded, on the basis of extensive experimental work, that the irritating substance of poison ivy is a glucoside, a compound of *rhamnose, gallic acid* and *fisetin*. To this substance the name *Toxicodendrin* is applied.

It is possible to obtain this active principle in the fluid extract of *Rhus toxicodendron*, an alcoholic extract of the fresh leaves of the plant, from which a tincture

[10] Pfaff, *Journal of Experimental Medicine*, 1897, Vol. 2, p. 181.

[11] Syme, "Some Constituents of the Poison Ivy Plant (*Rhus toxicodendron*)," Johns Hopkins University Dissertation, Baltimore, 1906.

is made and employed in a number of affections by a certain group of medical men. Pfaff had previously pointed out that the internal administration of toxicodendrol to rabbits killed them at the end of 12–15 days by nephritis, although some animals died in convulsions within the first 24 hours. The subcutaneous inoculation of the fluid extract of *Rhus toxicodendron* produced in rabbits an intense nephritis with large quantities of albumin and many casts in the urine, the animals dying in from 8 to 15 days. Rarely some of the rabbits died in convulsions on the first day. The effects of the fluid extract being identical with those described by Pfaff for toxicodendrol, there could be no doubt that this extract contained the active principle. In addition to the nephritis, a huge necrosis and slough developed at the site of the subcutaneous inoculation. Guinea-pigs are more susceptible to the poison than rabbits, a small quantity producing a similar local necrosis and nephritis. The fatal dose for rabbits varies from one half to two cubic centimeters, and for guinea-pigs from one fourth to one half cubic centimeter. With both species, if small doses be given at first, followed by increasing doses at appropriate intervals, active immunity can be established. Large quantities of the fluid extract can eventually be given, three to four cubic centimeters in guinea-pigs and eight to ten cubic centimeters in rabbits, in both cases representing a considerable multiple of a minimum fatal dose. The time of the dosage must be carefully graduated, the most favorable interval between the periods of administration being apparently ten to twelve days, corresponding to about the period of incubation. With low multiples of a fatal dose, the animals react well, develop no local lesions, and can be kept alive almost indefinitely, no late manifestations of intoxication appearing. If too large quantities be given, the animals die of nephritis, and occasionally local lesions are found. In general, however, the local action of the poison on the epithelial cells of the skin is less likely to appear during immunization than the destruction of the kidney cells.

The serum from these actively immunized animals will confer passive immunity upon other animals. For these experiments guinea-pigs were always selected because of their more regular susceptibility. The poison and serum must be administered separately to avoid the precipitation of the serum by the alcohol in the fluid extract, and even in the severe test of giving both doses at the same time the serum will completely neutralize the poison. In certain instances by this method of testing, one cubic centimeter of serum neutralized five or six fatal doses for guinea-pigs. When the effects of the *Rhus toxicodendron* are not completely obviated, the test animals die of nephritis. Careful dissection of the skin at the site of inoculation shows no necrosis or slough.[12]

In connection with the effect of *Rhus toxicodendron* upon the kidney in the production of active and passive immunity, it may be mentioned that the only human beings who have died as a result of ivy poisoning have apparently succumbed to kidney affections.

Large animals can also be immunized; a fifty-pound goat was eventually given twenty cubic centimeters without the development of subcutaneous lesions or nephritis.

Finally, it is interesting to inquire whether *natural immunity* to poison ivy occurs in man, and whether immunity develops after recovery from its effects. In regard to the first point, there is no difficulty in showing that many persons are

[12] Ford, *The Journal of Infectious Diseases*, Vol. 4, No. 4, November, 1907.

quite resistant to the action of the irritating substance. I know personally of a number of individuals who have been able since early childhood to handle poison ivy with impunity, no dermatitis resulting from contact with the fresh leaves. Opinions differ much in regard to the acquired immunity. Some people are extremely susceptible, the severest lesions following the slightest exposure. In many instances it is claimed that no immunity results from the first attack, a second, third or even a fourth attack of dermatitis occurring with painful regularity. A belief is common, moreover, that these subsequent attacks recur, without a second exposure, at the same season in which the first attack developed. There are, nevertheless, many cases in which a certain degree of immunity develops, the severe types of dermatitis never being reproduced, the subsequent exposure bringing out only a few vesicles and pustules on the skin.

It is interesting to speculate whether these cases of *natural immunity* are not really examples of *acquired immunity*, individuals in whom as children the effects of handling the ivy have gradually worn off, the original dermatitis having been so insignificant as to have escaped notice or being so many years distant as to be forgotten.

There is some evidence also as to the possibility of vaccinating against ivy poisoning. The internal administration of the tincture of *Rhus toxicodendron* is believed by many to completely prevent attacks of this affection, and in the survey for the Union Pacific Railway, when the line was pushed through a wild country much overgrown with the ivy, some of the engineers discovered that by chewing and swallowing the fresh leaves early in the spring, they could ward off attacks during the summer. It is stated that a similar precautionary measure is resorted to in the Adirondack Mountains, where the plant is so abundant as to be a troublesome pest.

In conclusion we have in the *Amanita phalloides* and in *Rhus toxicodendron* two poisonous substances, acting in one case upon the blood corpuscles, in the other upon the epithelial cells of the skin and kidney, in both of which the evidence at hand points to a glucoside as the carrier of the poisonous properties, and in both of which active and passive immunity may be experimentally produced. Whether these observations have anything more than theoretical value remains still to be determined, a practical application of these results being possible only when sera of considerable antitoxic power can be obtained from large animals.

Virulence of Pneumococci in Relation to Phagocytosis: E. C. ROSENOW.

Virulent pneumococci do not absorb opsonin from serum nor are they susceptible to phagocytosis, while non-virulent pneumococci absorb opsonins and are freely susceptible to phagocytosis. The pneumococci isolated from the blood in pneumonia resist phagocytosis in normal and pneumonic blood, while those isolated from the sputum are more susceptible and show a correspondingly lower grade of animal virulence. It seems that the pneumococci in the blood in lobar pneumonia are there because of their resistance to opsonification and phagocytosis.

The pneumococci isolated from the blood of cases of pneumococcus endocarditis are freely susceptible in vitro, to phagocytosis, both in normal and homologous blood, and yet in some way they are able to protect themselves against the action of the leucocyte and other cells in vivo because constantly present in the circulating blood. The recently isolated pneumococci in these cases when grown in the homologous serum from 24 to 48 hours instead of being

freely susceptible to phagocytosis, as is the case when grown in broth or upon agar, have become fairly resistant instead. When grown in normal serum they fail to acquire this resistance to the action of opsonin and the leucocyte.

Extracts from highly virulent pneumococci contain a substance or combination of substances which neutralize the opsonin in serum. This substance unites with virulent pneumococci quantitatively and by so doing confers upon them a degree of resistance to phagocytosis as well as to animal virulence. The extracted virulent pneumococci now acquire the power to absorb pneumococco-opsonin. In other words, it seems possible to extract from virulent pneumococci the substance upon which virulence probably depends and to which the name "virulin" has been given. While the action of virulin may be the subject of several hypothetical explanations, at present it is probably best to look upon it simply as a substance or mixture of substances which when united with the pneumococcal cell prevent the cell from taking up opsonin, and which substance, when free, has special affinity for opsonin. That it does not merely concern free opsinophile cell receptors seems likely because virulent pneumococci when extracted, that is, freed from virulence, are found to absorb pneumococco-opsonin freely.

The Mechanism of Streptococcus Immunity: Gustav F. Ruediger.

In a previous paper it was shown that, in test-tube experiments, suspensions of rabbit leucocytes in normal rabbit serum or blood destroy avirulent streptococci but not the virulent organisms. Suspensions of the leucocytes in heated serum or in 0.85-per-cent. NaCl solution do not destroy the avirulent streptococci. Dr. Hektoen and I have shown that the avirulent streptococci are freely taken up by rabbit leucocytes in normal serum, but the virulent organisms are not taken up. Washed rabbit leucocytes in heated serum or in 0.85-per-cent. NaCl solution do not ingest the avirulent streptococci.

Rabbits were now immunized according to Neufeld's method by injecting them first with a large dose of heated virulent streptococci and then with several doses of the living culture. These animals acquired an immunity so that they did not succumb to a subcutaneous injection of twice the minimum fatal dose of the streptococcus. In test-tube experiments it was now found that normal rabbit leucocytes, or washed leucocytes from an immune rabbit, when suspended in the immune rabbit serum, freely ingest the virulent streptococci. If, however, these leucocytes are suspended in normal rabbit serum they scarcely take up any of these streptococci. No difference could be detected between the normal leucocytes and those coming from an immune rabbit. The immunity is dependent upon a change in the serum, as the following experiment shows. Virulent streptococci were sensitized in the immune rabbit serum and another lot was treated similarly with normal serum. These cocci were suspended separately in salt solution and each suspension was added to a suspension of washed rabbit leucocytes in salt solution. It was found that the streptococci which had been sensitized in the immune serum were taken up by the leucocytes to the extent of eight per leucocyte, whereas those which had been sensitized in the normal serum were not taken up at all. That is, the serum had acquired something by virtue of which it was enabled to sensitize the virulent streptococci so that they were ingested by the rabbit leucocytes.

The immune rabbit serum does not possess anti-streptolytic properties.

Fourth Meeting.—Papers in joint session

with the Society of American Bacteriologists.

Program

"Passive Diphtheritic Immunity in Rabbits," by H. M. Goodman.

"The Changing Flora of Chronic Suppurations: Its Relation to Opsonotherapy," by A. P. Ohlmacher.

"Blackhead: A Coccidial Disease of Turkeys," by P. B. Hadley (by invitation).

"The Cause of the So-called Germicidal Property of Milk," by M. J. Rosenau and G. W. McCoy.

"The Significance of Leucocytes and Streptococci in the Production of a High-grade Milk," by Mary E. Pennington.

"A Note on the Occurrence of Leucocytes and Streptococci in Milk," by S. C. Prescott.

WILLIAM J. GIES,
Secretary

PUBLICATION IN GERMAN JOURNALS OF THE RESULTS OF AMERICAN CHEMICAL RESEARCH

IN the course of an address on "American Chemical Research," delivered before the American Chemical Society last June,[1] a brief reference was made to the practise of some American chemists of publishing the results of their investigations more or less systematically in German journals. Since the address was printed I have had opportunities of discussing the topic with various friends, several of whom publish in the manner indicated, and it has been suggested that it might be useful—and even interesting—to deal with the question at somewhat greater length.

It will, perhaps, be wise to state at the outset that, in my opinion, there can be no question as to the absolute *right* of an investigator to offer his results for publication when, where, how and to whom he pleases, but "all things that are lawful are not expedient," and it is really on this that the question turns. Closely interwoven with it are two other questions: Should the chemists of America combine to form a society? Should this society publish a journal?

The answers given by the chemists of the country have been unmistakably in the affirmative, consequently, it would appear to be the merest common-sense on the part of all interested, to endeavor to make both the society and its journal the best possible. It has sometimes been urged against the society that its admission requirements are too lenient and that it would be advantageous if its membership were limited to persons possessing some "qualification." Just what the nature of their "qualification" should be it is difficult to discover. Although this idea is, perhaps, attractive at the first glance, a little thought will show many serious objections to it. Only two of these need be mentioned at present. The one concerns the expenses of publication and is dealt with more fully below. The second objection may be expressed by saying that no society can be truly national in its scope and aims unless its membership includes all or nearly all of those professing the subject with which it deals. In the case of the American Chemical Society this battle has been fought and won. In numbers it ranks as the third largest association of chemists in the world and very soon it will take the second place. The fact that the names of all the better-known chemists of the country are on its roll proves that quality has not been sacrificed to quantity.

We may now consider the subject of publication. In his recent address to the American Chemical Society, during the Chicago meeting, President Bogert was understood to say that the *Journal of Physical Chemistry* and the *Journal of Biological Chemistry* have each a circulation of about 200, and that they do not pay their expenses; moreover, the editors give their services. No information could be

[1] SCIENCE, 26, 625 (1907).